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Letter to the Editor

Re: 'Ventricular arrhythmias induced by endothelin-1 or by acute ischemia: a comparative analysis using three dimensional mapping' (*Cardiovasc Res* 2000;45:310–320)

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Dear Editor,

We read with great interest the study by Becker et al. [1] in which they analyzed the three-dimensional activation patterns of ventricular arrhythmias induced by endothelin-1 (ET-1) in comparison with ischemia-induced arrhythmias. In order to support the hypothesis that ET-1 exerts an intrinsic arrhythmogenic effect which is not attributable to ischemia, the authors investigated the electrophysiologic effects and the mechanism of induced ventricular arrhythmias after intracoronary administration of ET-1, as compared to those caused by ligation of the left anterior descending artery. This study provides substantial information concerning proarrhythmic effects of ET-1 in vivo, and is of considerable interest to both clinical and basic electrophysiologists.

The findings are in accordance with the results of some previously published reports which demonstrated occurrence of severe ventricular arrhythmias during ET-1 administration even without a substantial reduction in coronary blood flow, any alterations on surface ECG, ischemic thermographic changes, or elevations in coronary sinus lactate concentrations [2]. Nevertheless, the topic remains to be controversial, and we believe that the findings do not suffice to conclude that ET-1 is directly arrhythmogenic for several reasons: First, using this methodology the authors cannot exclude the possibility that ET-1 infusion at a dose of 60 pmol/min may cause myocardial ischemia. In view of the peptide's marked vasoconstrictive potency, it is difficult to rule out some degree of accompanying regional, if not global, ischemia. Secondly, ET-1 and coronary ligation were similarly shown to cause all arrhythmias by focal mechanisms, suggesting abnormal automaticity and/or triggered activity as underlying mechanism. Furthermore, the arrhythmias originated mostly from the left ventricular subendocardium in both groups. The higher total number of arrhythmia episodes, prolonged conduction time and refractoriness, and involvement of macroreentrant mechanisms in the maintenance of some tachycardia episodes in the ligation group only suggests a more significant degree of ischemia, which is to be expected. The increased prevalence of right ventricular foci associated with increased duration of ET-1 infusion was explained by systemic recirculation of the agent. However, as the early pioneering work by de Nucci et al. showed, circulating ET-1 is substantially removed by the lungs and other organs [3]. Finally, it is well known that ventricular arrhythmias occur in two phases associated with distinct changes in the electrical tissue properties after occlusion of a major coronary artery in dogs, and the incidence of the arrhythmias may vary considerably because of marked variation in preexisting collaterals [4]. Therefore, interpretation of the results of this comparative analysis must be made with great caution.

The mechanisms by which ET-1 promotes the development of arrhythmias may include prolongation and increased dispersion of monophasic action potential duration, development of early after depolarizations, involvement of Ca^{2+}/K^{+} channels, generation of inositol triphosphate, acidosis, stimulation of the Na^{+}/H^{+} exchanger, and augmentation of cellular injury. However, all these mechanisms are all also activated by ischemia alone. Certainly, it is desirable to demonstrate a primary arrhythmogenic effect of ET-1, which may open a new era in the field of antiarrhythmic therapy. However, conclusive data is needed to prove the hypothesis, and it will be difficult to

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sort it out in view of the fact that increased secretion of ET-1 generally occurs in a complex substrate (ischemia/reperfusion, heart failure, etc.).

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